OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

Ottawa Hull K1A 0C9

(21) (A1) 2,142,871
(86) 1992/12/10
(43) 1994/03/03

(51) Int.Cl.[6] A61M 37/00

(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

6,020,8/33

(54) Printed Transdermal Drug Delivery Device

(72) Miranda, Jesus - U.S.A. ;
Cleary, Gary W. - U.S.A. ;

(71) Cygnus Therapeutic Systems - U.S.A. ;

(30) (US) 07/935,044 1992/08/25

(57) 19 Claims

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61F 13/00

A1

(11) International Publication Number: WO 94/04109

(43) International Publication Date: 3 March 1994 (03.03.94)

(21) International Application Number: PCT/US92/10672

(22) International Filing Date: 10 December 1992 (10.12.92)

(30) Priority data:
935,044 25 August 1992 (25.08.92) US

(71) Applicant: CYGNUS THERAPEUTIC SYSTEMS [US/US]; 400 Penobscot Drive, Redwood City, CA 94063 (US).

(72) Inventors: MIRANDA, Jesus ; 14714 Southwest 153rd Place, Miami, FL 33186 (US). CLEARY, Gary, W. ; 154 11th Avenue, San Mateo, CA 94401 (US).

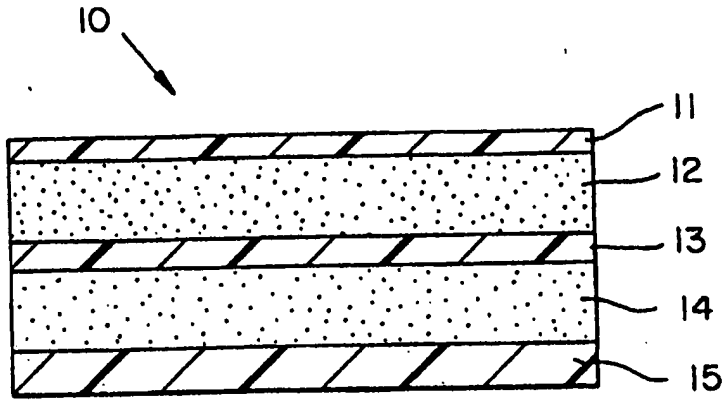
(74) Agents: BOZICEVIC, Karl et al.; Morrison & Foerster, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).

(81) Designated States: AU, CA, FI, JP, KR, NO, NZ, PT, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

2142871

(54) Title: PRINTED TRANSDERMAL DRUG DELIVERY DEVICE



(57) Abstract

A transdermal drug delivery device (10) which can be worn by a human patient for 24 hours while continuously delivering a drug to the patient for approximately 16 hours is produced by a particular method of manufacture. The device (10) is particularly useful with respect to the delivery of drugs which, if delivered for 24 hours, result in problems such as drug tolerance (e.g., nitroglycerin) or sleep disorders (e.g., nicotine). The drug is loaded into the device (10) in a concentration such that the drug becomes depleted from the device after approximately 16 hours to the extent that the rate of delivery of the drug to the patient is slowed to such an extent that the pharmacological effect of the drug on the patient becomes substantially nonexistent. The device (10) is in the form of a laminated composite that is adpated to be adhered to a predetermined area of unbroken skin or mucosal tissue. The individual layers of the device include an upper backing or "outer skin" layer (11), an anchor adhesive layer (12), a source layer (13) onto which the drug and/or vehicles are deposited initially, a contact adhesive (14) which is adapted to adhere to the skin or mucosa, and a release liner (15).

PRINTED TRANSDERMAL DRUG DELIVERY DEVICE

Cross-Reference to Related Applications

This application is a continuation-in-part of our earlier filed pending U.S. application Serial No. 07/769,155, filed September 27, 1991, which is a continuation of U.S. application Serial No. 07/453,617, filed December 20, 1989 (abandoned), which is a divisional of U.S. application Serial No. 07/215,074, filed July 5, 1988 (U.S. Patent 4,915,950), which is a continuation-in-part of U.S. application Serial No. 07/155,327, filed February 12, 1988 (abandoned), all of which applications are incorporated herein by reference and to which applications we claim priority under 35 U.S.C. §120.

Field of the Invention

This invention relates generally to transdermal delivery devices and to methods of making and using such devices. More particularly the invention relates to transdermal nicotine delivery systems which include particular amounts of nicotine within a matrix allowing the device to be worn for 24 hours but be depleted of nicotine to the extent that nicotine is not further delivered to the patient after a period of about 16 hours.

Background of the Invention

A variety of devices have been proposed or used for administering drugs transdermally. These devices are generally in the form of a bandage or skin patch that includes a reservoir that contains the drug and a pressure-sensitive adhesive component by which the device is attached to the skin. Depending upon the inherent permeability of the skin to a particular drug, the device may also include means for coadministering a percutaneous absorption enhancer or an element, such as a membrane interposed between the reservoir and the skin, that regulates the rate at which the drug or the percutaneous absorption enhancer is administered to the skin.

The commercially available techniques for manufacturing these devices involve conventional casting and laminating processes. Actual incorporation of the drug is typically effected by (1) admixture of the drug with a compatible solvent, (2) incorporation of the drug into the drug reservoir by immersion in the drug/solvent admixture, and (3) evaporation of the solvent. In practice, this method has proved to have several disadvantages.

First, for many drugs, the solvent selected is necessarily organic, rather than aqueous. As many organic solvents are flammable and/or toxic, an element of risk is thus introduced into device fabrication and use. Another shortcoming is that with volatile drugs or drugs that are sensitive to heat, evaporation of the solvent can either volatilize or degrade the drug. The present invention is addressed to these shortcomings, and provides a device fabrication process which eliminates the necessity for both organic solvents and high-temperature evaporation. The process minimizes drug degradation and loss to the environment, while eliminating the possibility of contamination with organic residues

which may be harmful to the skin, e.g., as irritants, sensitizers, carcinogens, or the like.

Furthermore, conventional casting is done in solid sheets or stripes. When laminated and die cut out, the remaining web is left unusable and is discarded. Highly expensive drugs are costly to discard, as dangerous or controlled narcotic drugs can be delivered for abuse or present other uncontrollable hazards. By carrying out the method disclosed herein it is possible to eliminate some of the disadvantages of earlier methods and provide a system which can include a precise amount of a drug which, after use, will be depleted of the drug to the extent that further drug could not be delivered to the patient, thus reducing the costs, potential dangers and potentials for abuse.

Most drug delivery devices are designed so that they can be worn for 24 hours. The 24-hour wear period provides for good patient compliance in that the patient can replace the patch each day at approximately the same time. Further, most patches are designed so as to continually deliver a particular drug to the patient during the entire 24-hour period. Although the once a day dosing regime is desirable, the continuous delivery of drug to a patient over a 24-hour period is often not desirable. Problems related to the continuous delivery of the drug to the patient over a 24-hour period varied depending on the type of drug. With respect to certain drugs the problem becomes one of tolerance, i.e., the patient becomes less reactive to larger and larger amounts of drugs in that the drugs are continually being delivered. Tolerance is a problem with drugs such as narcotics and nitroglycerin used as a vasodilator. With other drugs, such as nicotine the continuous delivery of the nicotine to the patient can result in problems such as sleep disorders, skin irritation and

the like (see D.M. Daughton et al., Arch. Intern. Med. 151:749-752 (1991) and K.O. Fagerstrom et al., J. Smoking Related Dis., in press). The present invention addresses these problems by loading specific amounts of the drug into the device such that the drug will be substantially depleted from the patch after a given period of time, i.e., the drug is depleted from the patch to the extent that drug is no longer delivered to the patient even though it may remain in the patch.

Because the fabrication process does not involve the use of high temperatures, it is also useful in incorporating volatile vehicles, excipients or enhancers into transdermal delivery devices. In addition, a device may be fabricated using the present process so as to contain a volatile fragrance. Such a device is designed to exude fragrance over a protracted, predetermined period of time.

Summary of the Invention

Transdermal delivery devices are disclosed which include a backing layer which is substantially impermeable to the drug, and a drug matrix layer which may be in the form of a pressure-sensitive pharmaceutically acceptable contact adhesive having the drug dispersed therein. The drug is loaded into the drug matrix layer in an amount such that the drug will, after about 14-18 hours (preferably 16 hours) of contact with the patient, be depleted of the drug to the extent that delivery of the drug to the patient is slowed to a rate such that the effect of the drug on the patient is negligible. To achieve this effect the loading amount of the drug into the drug matrix layer is closely controlled and varies somewhat depending on the particular drug in that different drugs have different rates of delivery. For example, when the system is designed to deliver nicotine, the nicotine

is loaded into the drug matrix layer in an amount in the range of about 0.70 to about 1.15, more preferably 0.75 to 0.95 mg/cm^2. By placing a drug delivery system of the invention on a patient there is provided a method of drug delivery whereby the patch is placed on the patient for a period of 24 hours during which time the drug is delivered to the patient during only about 14-18 hours (preferably about 16 hours) after which the drug is depleted from the patch to the extent that any further delivery to the patient is so insignificant as to not have any detectable pharmacological effect on the patient.

The delivery devices of the invention are obtained by a method comprising:

(a) laminating an adsorbent source layer to a pressure-sensitive, pharmaceutically acceptable contact adhesive layer, the contact adhesive layer comprised of a material that is permeable to the drug and which defines a basal surface for adhesion to skin;

(b) depositing a drug in liquid form on one face of the adsorbent source layer;

(c) laminating an anchor adhesive layer to the opposing face of the source layer; and

(d) applying a backing layer to the anchor adhesive layer which defines the upper surface of the device and is substantially impermeable to the drug.

A preferred embodiment of the invention is a transdermal drug delivery device for administering nicotine to a human patient transdermally and continuously for a period of approximately 16 hours. The device is comprised of a backing layer which is substantially impermeable to nicotine, which backing layer defines the upper surface of the device. The device is further comprised of an anchor adhesive layer which is adjacent to the backing layer and laminated thereto. Thereafter, a layer of pressure-

sensitive, pharmaceutically acceptable, contact adhesive which is permeable to nicotine is provided. This pressure-sensitive adhesive layer defines the basal surface of the device which is adhered to the skin of the patient. The device is also preferably comprised of an adsorbent source layer which is in contact with and contained between the anchor adhesive layer and layer of pressure-sensitive adhesive. The nicotine is preferably dispersed uniformly throughout the layer of pressure-sensitive contact adhesive in an amount such that the nicotine in the device will, after 16 hours of contact with the patient, be depleted to the extent that the delivery of the nicotine to the patient is slowed to a rate such that the effect of the nicotine on the patient is negligible, i.e., no pharmacological detectable effect. The amount of nicotine is preferably in the range of 0.75 to 0.95 mg/cm^2 but can vary outside that range in an amount of about 25% ±.

In still another aspect of the invention, a method and device similar to the aforementioned are provided for the incorporation and release of fragrance. In such a case, the fragrance is initially deposited onto the source layer and then released over time through the adhesive and backing layers which are selected so as to be permeable to the fragrance.

A key advantage of the present invention is in the "printing" of the selected drug, drug-vehicle combination, or other material, in liquid form, on the adsorbent source layer in a particular amount. That is, the material is loaded into the device by substantially uniform deposition on the surface of the source layer. For many materials, this one-step deposition eliminates the need for organic solvents as well as the need for heat treatment.

After loading of the drug onto the source layer, the drug migrates into the underlying contact

adhesive layer and, depending on the material selected for the anchor adhesive layer, into that layer as well. The release kinetics of the drug into the skin from the contact adhesive layer are determined by the degree of drug loading (which can be at, above, or below saturation in this system) and the diffusivity and solubility of the drug in the two adhesive layers. The source layer thus serves to initially retain the deposited drug which then migrates from the source layer into one or both adhesive layers.

Brief Description of the Drawings

Figure 1 shows a partly schematic, sectional view of a transdermal drug delivery device according to the invention.

Figure 2 shows an apparatus which may be used in fabricating a transdermal drug delivery device according to the method of the invention.

Figure 3 shows the in vitro permeation of nicotine through human cadaver skin from a transdermal drug delivery device fabricated according to the presently disclosed method.

Detailed Description of the Invention

Before the present transdermal delivery device, method of delivering drugs and method of manufacturing such devices is described, it is to be understood that this invention is not limited to the particular devices, methods and processes described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular devices, methods and processes only, and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims.

It must be noted that as used in this specification and in the appended claims, the singular

forms "a", "an" and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a drug permeation enhancer" includes mixtures of such permeation enhancers, reference to "an adhesive" includes mixtures of adhesives and reference to "the method of delivery" includes one or more methods of delivery of the general type described herein and of a type which would be deduced by those skilled in the art upon reading this disclosure.

Before providing a detailed description of the invention, the following definition of terms will be provided.

1. Definitions:

By "printed" as used herein to describe the method of incorporating a drug or other material into the source layer is meant a substantially uniform deposition of the drug, in liquid form, onto one surface of the source layer. As the source layer comprises a porous material, the drug is initially retained by that layer, i.e., prior to equilibration, and then diffuses into one or both of the adjacent layers. It will be appreciated by those skilled in the art that a variety of techniques may be used to effect substantially uniform deposition of material, e.g., Gravure-type printing, extrusion coating, screen coating, spraying, painting, or the like.

By a drug in "liquid form" as used herein is meant either a drug that is itself a liquid or a drug which is suspended, dissolved or dispersed in a selected solvent. Solvents may or may not be aqueous, depending on the particular drug used, and may include commonly used liquid vehicles and skin penetration enhancers. Preferred solvents are nonaqueous and selected so that they can be incorporated into the final system without adverse effect.

By "pharmaceutically acceptable" material as used herein is meant a material which does not interfere with the biological effectiveness of the drug administered and which is not for any reason biologically or otherwise undesirable.

By a "permeable" adhesive is meant a material in which the selected drug has at least moderate solubility and diffusivity, i.e., drug solubility ont he order of 5 to 50 wt.%, preferably 10 to 30 wt.%, and diffusivity in the range of about 1 x 10^{-6} to about 1 x 10^{-12} cm^2/sec.

By "substantially impermeable" as used herein to describe the backing layer is meant that an effective amount of the selected drug will be contained within the device without loss of any substantial amount through the backing layer. It should be noted that where the device is used for the release of fragrance, however, the backing layer is, by contrast, permeable to the fragrance. In such an embodiment, the device thus allows for release of fragrance into the atmosphere.

Description of the Transdermal Drug Delivery Device

Referring now to Figure 1, the transdermal drug delivery device provided by the present method is shown generally at 10. The device is designed specifically for transdermal administration of a drug at controllable, therapeutically effective rates. The device 10 is in the form of a laminated composite that is adapted to be adhered to a predetermined area of unbroken skin or mucosal tissue. The individual layers of the device include an upper backing or "outer skin" layer 11, an anchor adhesive layer 12, a source layer 13 onto which the drug and/or vehicles are deposited initially, a contact adhesive 14 which is adapted to adhere to the skin or mucosa, and a release liner 15.

The backing layer 11 functions as the primary structural element of the device and provides the device with much of its flexibility, suitable drape, and, where necessary, depending upon the material incorporated into the device, occlusivity. In the preferred embodiment in which the device serves as a transdermal drug delivery system, the backing layer also serves as a protective covering to prevent loss of the drug (and/or vehicle, solubilizer or permeation enhancer, if present) via transmission through the upper surface of the device. (In the alternative embodiment in which the device serves as a fragrance patch, as noted above, the backing layer will by contrast allow release of fragrance into the atmosphere.) Backing layer 11 may also be used to impart the device with a desirable or necessary degree of occlusivity which in turn causes the area of skin on which the device is placed to become hydrated. In such a case, a layer is selected that has a level of water vapor transmissibility that makes the device occlusive to the degree required to cause the area of skin to be hydrated. It is then preferable that the device provide at least about 90% hydration, more preferably at least about 95% hydration of the skin, as measured by a dielectric hydration probe available from Dr. Howard Maibach, U.C.S.F., San Francisco, California. Such occlusivity is desirable when drugs such as estradiol or other steroids are being administered. If the drug being administered is such that skin hydration is not necessary or desirable, it is preferable to use layers that provide a composite that is "breathable", i.e., transmits water vapor from the skin to the atmosphere. Such breathability contributes to the nonocclusive nature of the composite and lessens the likelihood that the area of skin on which the composite is worn will become highly hydrated and irritated.

Backing 11 is preferably made of a sheet or film of a preferably flexible elastomeric material that is substantially impermeable to the selected drug. The layer is preferably on the order of 0.0005" to 0.003" in thickness, and may or may not contain pigment. The layer is preferably of a material that permits the device to mimic the contours of the skin and be worn comfortably on areas of skin, such as at joints or other points of flexure, that are normally subjected to mechanical strain with little or no likelihood of the device disengaging from the skin due to differences in the flexibility or resiliency of the skin and the device. Examples of elastomeric polymers that are useful for making layer 11 are polyether block amide copolymers (e.g., PEBAX copolymers), such as NUKRELL polymers, polyurethanes such as PELLATHANE or ESTANE polymers, silicone elastomers, polyester block copolymers that are composed of hard and soft segments (e.g., HYTREL polymers), rubber-based polyisobutylene, styrene, and styrene-butadiene and styrene-isoprene copolymers. Polymers that are flexible include polyethylene, polypropylene, polyesters, e.g., polyester terephthalate (PET), which may be in the form of films or laminates. The preferred polymer used for the backing will depend on the material or drug incorporated into the device and on the nature of any vehicles, solubilizers, or the like that are used.

Anchor adhesive layer 12 adheres to backing layer 11 and to source layer 13. The anchor adhesive is preferably but not necessarily of a material in which the selected drug or vehicle has moderate solubility and diffusivity. In such a case, after equilibration, the drug will have diffused not only into the contact adhesive layer 14, but also into the anchor adhesive. Diffusion into both adhesive layers is useful insofar as regulation of release kinetics is

concerned. That is, by careful selection of the materials used for the anchor and contact adhesive layers, the distribution of drug throughout the entire system can be regulated. This is because the release kinetics of the drug from the device can be controlled by the diffusivity and solubility of the drug in both of the adhesive layers as well as in backing layer 11. When the drug is below saturation in all layers, the total drug loading controls the release kinetics.

An important aspect of the invention is providing for a specific range of drug loading which will allow the drug to be delivered to the patient over a period of about 14-18 hours (preferably 16 hours) even though the device is worn by the patient for 24 hours. This is accomplished by including a particular concentration of the drug into a layer such as the pressure-sensitive contact adhesive layer. The concentration of the drug within this layer will vary somewhat depending upon the particular drug being delivered. In connection with the present invention it has been found that it is necessary to include nicotine in a concentration within the range of about 0.70 to about 1.15 mg/cm^2, preferably 0.75 - 0.95 mg/cm^2 and most preferably about 0.83 mg/cm^2. By including nicotine in the adhesive layer in this concentration and placing the patch on the patient the nicotine will be delivered to the patient for approximately 16 hours, after which the drug will be depleted from the delivery system to the extent that the rate of delivery of the drug to the patient is slowed to such an extent that the delivery of nicotine to the patient becomes negligible, i.e., no detectable pharmacological effect. The nicotine may be in the form of a free base or a salt and a particularly useful salt is nicotine monoacetate. The concentration of any particular drug in the adhesive layer will vary somewhat depending on the permeability

of that drug to human skin and also somewhat based on the adhesive material.

Examples of suitable materials for anchor adhesive layer 12 include polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low molecular weight polyether block amide copolymers (PEBAX copolymers), tacky rubbers such as polyisobutene, polystyrene-isoprene copolymers, polystyrene-butadiene copolymers, and mixtures thereof. The particular polymer(s) used for the anchor adhesive layer will depend on the drug, vehicle, enhancer, etc., selected. The thickness of the anchor adhesive layer may vary but is typically in the range of about 0.0005" to about 0.005". In the case of a fragrance patch, the material serving as the anchor adhesive layer should, like the backing layer, be selected so as to be substantially permeable to the fragrance incorporated into the patch.

Source layer 13 is a thin, flexible layer of an adsorbent material which provides the surface on which the drug is printed or otherwise deposited. The source layer allows the liquid drug (together with vehicle, solubilizer or the like) to be printed on its surface as a result of having surface properties not found in either the contact or anchor adhesive layers. During fabrication, the drug is deposited in liquid form onto one face of this layer in a substantially uniform pattern. The drug must wet the surface in such a way that squeezing of liquid to the periphery of the device during lamination is substantially prevented. The material is selected so that the drug is adsorbed, rather than absorbed, by the layer, since the drug must be available to migrate into contact adhesive layer 14 and preferably into anchor adhesive layer 12 as well. The source layer is preferably of a non-woven fabric, e.g., polyester, polyethylene,

polypropylene, polyamides, rayon or cotton, and a particularly preferred material for the source layer is a 100% non-woven polyester. Woven fabrics, however, can also be used if desired. The thickness of the source layer may vary, but is preferably in the range of about 0.001" to 0.010".

It should be pointed out that the source layer does not serve as a drug reservoir; the drug is only transiently adsorbed by the source layer pending equilibration, i.e., migration into one or both of the adjacent adhesive layers.

Alternatively, the inner surface of either the anchor or contact adhesive layers may be treated and thus itself serve as the source layer for purposes of drug deposition. Still another alternative is to use a contact or adhesive layer that has a porous surface, enabling the drug to be printed "into" the surface pores. Contact adhesive layer 14, which plays the principal role in determining the rate at which drug is released from the device, is a pressure-sensitive skin contact adhesive comprised of a pharmaceutically acceptable material. Like source layer 13, it must be chemically and physically compatible with the drug and with any enhancer used. Further, the drug selected must have at least moderate solubility and diffusivity in this layer, since the drug must be able to readily migrate from source layer 13 into and through contact adhesive layer 14 and to the skin. The thickness of the contact adhesive layer is preferably in the range of about 0.0005" to about 0.005".

Suitable materials for contact adhesive layer 14 include those enumerated for anchor adhesive 12. It is possible (in some cases) to use materials for the contact adhesive layer that are relatively impermeable to the drug, e.g., where the diffusivity of the drug through skin is quite high. In the case

of a fragrance patch, contact adhesive layer 14 may or may not be permeable to the fragrance. In any particular device fabricated according to the present process, the materials chosen for the contact and anchor adhesive layers may be the same or different.

Prior to use, device 10 includes a release liner 15. Just prior to use, this layer is removed from the device to expose contact adhesive layer 14. The release liner will normally be made from a drug/vehicle/enhancer impermeable material that is inherently "strippable" or rendered so by techniques such as silicone or fluorocarbon treatment.

Device 10 need not include a means for controlling the rate at which either the drug or the enhancer is administered to skin. Instead, the release kinetics of the drug from the bandage can be controlled by the materials selected for the anchor and contact adhesive layers and by the degree of drug loading. Either the contact adhesive layer or the source layer could be rate-controlling, depending on the drug and materials selected. Alternatively, the drug and/or vehicle microencapsulated to provide controlled release could be deposited on the source layer prior to lamination, i.e., instead of deposition of the drug in "liquid form" as previously defined. Typically, over the effective lifetime of the device, the drug is presented to the skin at a rate in excess of the rate that the treated area of skin is able to absorb. It will be appreciated, however, that depending upon the particular drug (and enhancer when one is needed) that is being administered, that it may be necessary or desirable to include an element in the device that will control the release rate of the drug and/or the enhancer. Such elements are known in the art. The most common is a polymer membrane having appropriate drug/enhancer permeability properties

interposed between the source layer and the contact adhesive layer.

The term "drug" as used to describe the principal active ingredient of the device intends a biologically active compound or mixture of compounds that has a therapeutic, prophylactic or other beneficial pharmacological and/or physiological effect on the wearer of the device. Examples of types of drugs that may be used in the inventive device are anti-inflammatory drugs, analgesics, antiarthritic drugs, tranquilizers, narcotic antagonistis, antiparkinsonism agents, anticancer drugs, immunosuppression agents, antiviral agents, antibiotic agents, appetite suppressants, antiemetics, anticholinergics, antihistaminics, antimigraine agents, coronary, cerebral or peripheral vasodilators, anti-anginals, e.g., calcium channel blockers, hormonal agents, contraceptive agents, antithrombotic agents, diuretics, antihypertensive agents, cardiovascular drugs, chemical dependency drugs, and the like. The appropriate drugs of such types are capable of permeating through the skin either inherently or by virtue of treatment of the skin with a percutaneous absorption enhancer.

Because the size of the device is limited for patient acceptance reasons, the preferred drugs are those which are effective at low concentration in the blood stream. Examples of specific drugs are steroids such as estradiol, progesterone, norethindrone, norethindrone acetate, levonorgestrel, ethynodiol diacetate, norgestamate, gestadene, desogestrel, 3-keto desogestrel, demegestone, promegestrone, testosterone, hydrocortisone, and their esters; nitro compounds such as amyl nitrate, nitroglycerine and isosorbide nitrates; amine compounds such as nicotine, chlorpheniramine, terfenadine and triprolidine; oxicam derivatives such

as piroxicam; mucopolysaccharidases such as thiomucase; opioids such as buprenorphine, fentanyl and fentanyl derivatives or analogs, naloxone, codeine, dihydroergotamine, pizotiline, slabutamol and terbutaline; prostaglandins such as those in the PGA, PGB, PGE and PGF series, e.g., misoprostol and enprostil, omeprazole, imipramine; benzamides such as metoclopramine and scopolamine; peptides such as growth releasing factor, growth factors (EGF, TGF, PDGF and the like), and somatostatin; clonidine; dihydropyridines such as nifedipine, verapamil, diltiazem, ephedrine, propanolol, metoprolol and spironolactone; thiazides such as hydrochlorothiazide and flunarizine; sydononimines such as molsidomine; sulfated polysaccharides such as heparin fractions; and the salts of such compounds with pharmaceutically acceptable acids or bases, as the case may be.

It should be noted that the present method and device are suitable for use with volatile drugs and excipients, as no heat treatment step is involved or necessary. Thus, the present invention is useful with drugs such as nicotine, nitroglycerin, amyl nitrate, and scopolamine. The present device is also useful with drugs such as fentanyl, which will typically be incorporated into the patch using nonaqueous, volatile vehicles and/or enhancers which, because they volatilize during heat treatment, have proven difficult to incorporate into a transdermal delivery device by conventional means.

Since the inherent permeability of the skin to some drugs, such as steroids, is too low to permit therapeutic levels of such drugs to pass through a reasonably sized area of unbroken skin, it is necessary to coadminister a percutaneous absorption enhancer with such drugs. Accordingly, in such a case, a percutaneous absorption enhancer will be present in the device along with the drug, i.e., will

be initially deposited on source layer 13 together with the drug. In addition to affecting the permeability of the skin to the drug, the enhancer may also increase the diffusivity of the drug in the source layer and in the adhesive layers, thus increasing the permeability of the device as a whole to the drug. Any number of the many percutaneous absorption enhancers known in the art may be used in conjunction with the present invention. For examples of suitable enhancers, see U.S. Patents Nos. 3,996,934; 4,460,372; 4,552,872; 4,557,934 and 4,568,343 and the patents referenced therein.

When the inventive device is used to administer drugs to which the permeability of the skin is inherently too low to allow passage of therapeutic amounts of the drug, enhancers will be included in the device, "printed" onto the source layer along with the drug or incorporated into one or both of the adhesive layers. Correlatively, when the device is used to administer a drug to which the permeability of the skin is inherently sufficient to pass therapeutic amounts, it is not necessary to coadminister an enhancer. Thus, in general terms, the inclusion of an enhancer in the device is optional, depending on the particular drug that is being administered.

Processes of Making the Transdermal Devices

The device of the present invention is readily manufactured as follows. As illustrated by Figure 2, anchor adhesive 12 may be roll-coated onto a backing layer 11 of a commercially available film at a coating weight in the range of about 0.2 mg/cm^2 to 15 mg/cm^2, more preferably in the range of about 1 mg/cm^2 to 10 mg/cm^2. Similarly, the pressure-sensitive skin contact adhesive 14 may be coated onto release liner 15 at a coating weight in the range of 0.2 mg/cm^2 to 15 mg/cm^2, more preferably 1 mg/cm^2 to 10 mg/cm^2. The

source layer 13 is then deposited onto either contact adhesive layer 14 or onto anchor adhesive 12, preferably onto the contact adhesive. The selected drug in liquid form (optionally admixed with enhancer), is then printed onto the exposed surface of source layer 13 using conventional printing techniques. In an alternative embodiment of the invention, the drug is initially contained in one or both of the anchor and contact adhesive layers (e.g., by incorporation of the drug into the layers prior to lamination), and enhancer and/or vehicle is printed onto the source layer.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make the transdermal drug delivery devices of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, concentrations, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, concentrations are milligrams per square centimeter of device, temperature is in degrees centigrade and pressure is at or near atmospheric.

Example 1

A bandage for delivering nicotine transdermally for approximately 16 hours was prepared as follows. The anchor adhesive was coated onto a facestock of about 0.0015" flexible polyester laminate at a coating weight of 6.5 mg/cm^2. The composition of the anchor adhesive was approximately 1:5:2

polyisobutylene, m.w. 1.2 x 10^6/ polyisobutylene, m.w. 35,000/ polybutene blend, m.w. 2300. The pressure-sensitive contact adhesive having the same composition as the anchor adhesive layer was coated, also at 6.5 mg/cm^2, onto a 0.003" siliconized polyester release liner. The source layer, a 100% non-woven polyester fabric at 4.2 mg/cm^2, was then laminated to the anchor adhesive. Nicotine free base was deposited, neat, onto the source layer using a fine mist airbrush in a uniform pattern, at about 0.9 mg/cm^2. The contact adhesive/release liner composite was then laminated onto the exposed surface of the drug reservoir, forming a laminate of the final device as shown in Figure 1. Individual devices were die cut from the laminated product. The resulting in vitro skin permeation over 13 hours is shown in Figure 3.

Example 2

Example 1 was repeated, except that prior to deposition the nicotine was diluted with freon to a concentration of 10 wt.% to facilitate dispersal in the source layer. After deposition, the freon is removed by blowing warm air (about 30°C) over the laminate for about 2 minutes.

Example 3

A bandage for delivering nitroglycerine was made in a manner similar to that described in Example 1 for the nicotine bandage. The nitroglycerine was deposited onto the source layer as a 10% solution in ethanol using polyethylene glycol monolaurate (PGML) as carrier. The ethanol was allowed to evaporate and the final laminate was prepared as described in Example 1.

Example 4

A transdermal device for delivering nicotine monoacetate transdermally for approximately 16 hours was prepared as follows. A first subassembly PIB adhesive was coated onto a facestock of a 12.5 micron flexible polyester film at a coating weight of 4.0 mg/cm^2. The PIB adhesive was coated, also at 4.0 mg/cm^2, onto a 0.003" siliconized polyester release liner to provide a second subassembly. A 100% polyester non-woven fabric at 35 g/yd^2 was then laminated to the PIB adhesive of the first assembly. Nicotine monoacetate was deposited, neat, onto the fabric in a uniform pattern, at about 1.1 mg/cm^2. The second subassembly composite was then laminated onto the exposed surface of the drug-containing fabric forming a five-layer laminate. Individual devices were die cut from the laminated composite.

The instant invention has been shown and described herein in what is considered to be the most practical, and preferred embodiments. It is recognized, however, that departures may be made therefrom which are within the scope of the invention, and that obvious modifications will occur to one skilled in the art upon reading this disclosure.

CLAIMS

1. A transdermal drug delivery device for administering a drug to a human patient, transdermally and continuously for a period of approximately 14 to 18 hours, the device being comprised of a laminated composite, comprising:

(a) a backing layer that is substantially impermeable to the drug, which backing layer defines an upper surface of the device; and

(b) a layer of a pressure-sensitive, pharmaceutically acceptable, contact adhesive which is permeable to the drug, and which defines a basal surface of the device to be adhered to the skin of the human patient;

wherein the drug is dispersed throughout the adhesive and is present in a concentration such that the drug will be delivered in a pharmacologically effective amount for about 14 to 18 hours but, after 14 to 18 hours of contact with the skin of the patient, will be depleted to the extent that delivery of the drug to the patient is slowed to a rate such that the effect of the drug on the patient is negligible when the device is in contact with the skin for a total of about 24 hours.

2. The device of claim 1, wherein the drug is nicotine.

3. The device of claim 2, wherein the nicotine is dispersed in the adhesive in an amount in the range of 0.70 to about 1.15 mg/cm^2.

4. The device of claim 3, wherein the nicotine is dispersed in the adhesive in an amount in the range of 0.75 to 0.95 mg/cm^2.

03 Rec'd PCT/ 11 OCT 1994

5. The device of claim 4, wherein the nicotine is dispersed in the adhesive in an amount of about 0.83 mg/cm².

6. The device of claim 1, wherein the drug is nicotine, the nicotine is delivered continuously for a period of approximately 16 hours, and the nicotine is dispersed in the adhesive in an amount in the range of about 0.75 to 0.95 mg/cm².

7. A transdermal drug delivery device for administering nicotine to a human patient transdermally and continuously for a period of approximately 14 to 18 hours, the device being in the form of a laminated composite, comprising:

(a) a backing layer that is substantially impermeable to nicotine, which defines the upper surface of the device;

(b) an anchor adhesive layer adjacent to the backing layer and laminated thereto;

(c) a layer of a pressure-sensitive, pharmaceutically acceptable contact adhesive which is permeable to nicotine, and which defines the basal surface of the device to be adhered to the skin of the human patient; and

(d) a porous adsorbent source layer in contact with and contained between layers (b) and (c),

wherein the nicotine is dispersed throughout said contact adhesive layer and is present within the laminated composite at a loading of in the range such that the nicotine in the device will be delivered in a pharmacologically effective amount for about 14 to 18 hours but, after 14 to 18 hours of contact with skin of the patient, will be depleted to the extent that delivery of nicotine to the patient is slowed to a rate such that the pharmacological effect of the nicotine on the patient

is negligible when the device is in contact with the skin for a total of about 24 hours.

8. The device of claim 7, wherein the nicotine is present in the pressure-sensitive adhesive in an amount in the range of about 0.75 to about 0.95 mg/cm^2 and is delivered continuously for a period of about 16 hours.

9. The device of claim 7, wherein the nicotine is present in the form of nicotine free base.

10. The device of claim 7, wherein the nicotine is present as a salt.

11. The device of claim 10, wherein the nicotine salt is nicotine monoacetate.

12. The device of claim 7, wherein the contact adhesive layer and the anchor adhesive layer are substantially permeable to the nicotine.

13. The device of claim 7, wherein the anchor adhesive layer comprises polyisobutylene.

14. The device of claim 7, wherein the anchor adhesive layer comprises a mixture of polyisobutylene and polybutene.

15. The device of claim 7, wherein the contact adhesive layer comprises polyisobutylene.

16. The method of claim 7, wherein the contact adhesive layer comprises a mixture of polyisobutylene and polybutene.

17. The device of claim 7, wherein the source layer comprises a nonwoven fabric.

18. The device of claim 17, wherein the nonwoven fabric is comprised of polyester.

19. A transdermal drug delivery device for administering nicotine to a human patient transdermally and continuously for a period of approximately 16 hours, the device being in the form of a laminated composite, comprising:

(a) a backing layer that is substantially impermeable to nicotine, which defines the upper surface of the device;

(b) an anchor adhesive layer adjacent to the backing layer and laminated thereto, comprising a composition selected from the group consisting of polyisobutylene and a mixture of polyisobutylene and polybutene;

(c) a layer of a pressure-sensitive, pharmaceutically acceptable contact adhesive which defines the basal surface of the device to be adhered to the skin of the human patient; and

(d) an adsorbent, nonwoven fabric layer in contact with and contained between layers (b) and (c),

wherein the nicotine is selected from the group consisting of nicotine free base and nicotine monoacetate, and is dispersed throughout said contact adhesive layer and is present within the laminated composite at a loading of in the range such that the nicotine in the device will be delivered in a pharmacologically effective amount for approximately 24 hours but, after 16 hours of contact with skin of the patient, will be depleted to the extent that delivery of nicotine to the patient is slowed to a rate such that the pharmacological effect of the nicotine on the patient is

PCT/US 92/10672

11 OCT 1994

negligible when the device is in contact with the skin for a total of about 24 hours.

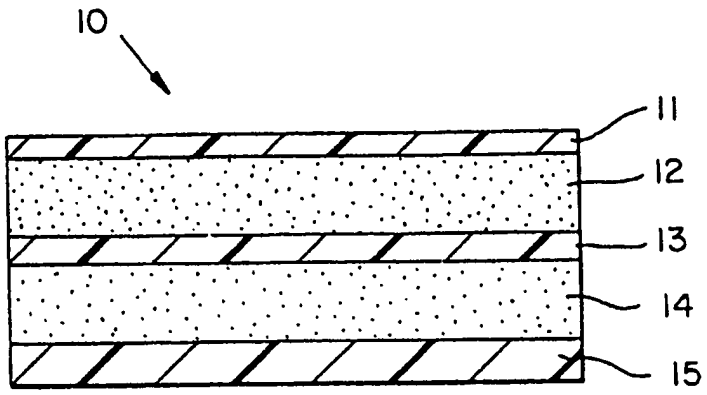

10
11
12
13
14
15

FIG. 1

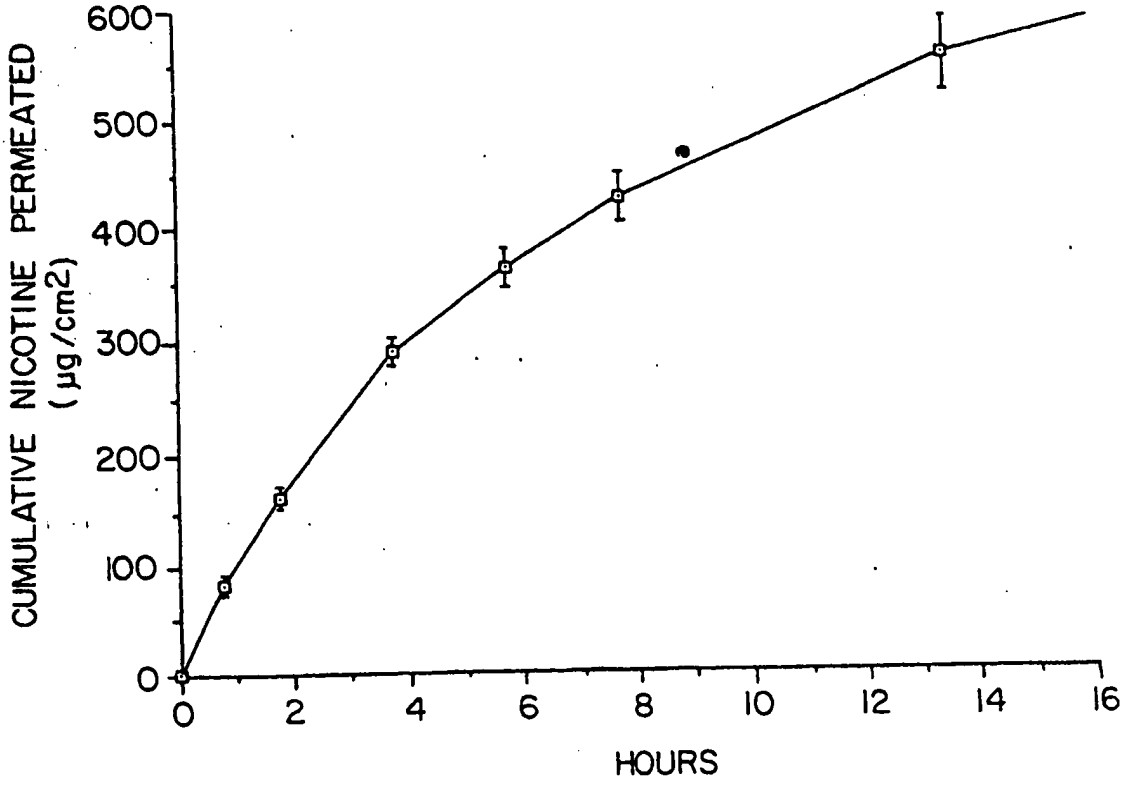

CUMULATIVE NICOTINE PERMEATED (µg/cm2)
600
500
400
300
200
100
0
0
2
4
6
8
10
12
14
16
HOURS

FIG. 3

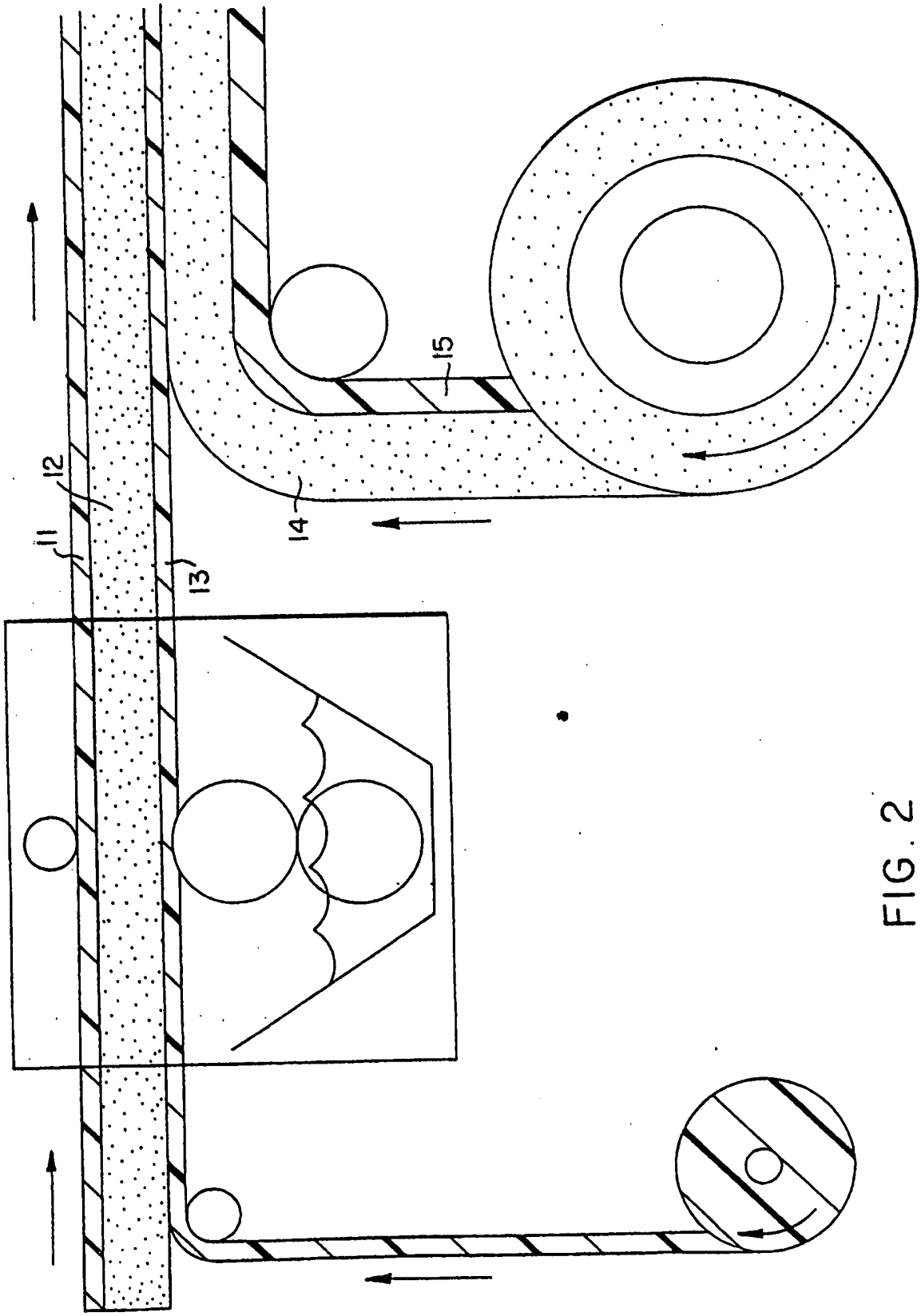


FIG. 2